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## **Relationship Between Rhinitis, Asthma, and Eczema and the Presence of Sensitization in Young Swiss Adults**

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**Abstract:** Background: Rhinitis is a very common disease with allergies being the most frequent causative factor. It can co-occur together with asthma and eczema in atopic as well as in nonatopic patients. Objectives: To assess the prevalence of allergic sensitization within patient groups with rhinitis in consideration of the co-occurring disorders of asthma and eczema. Methods: Students of the third year of medical school completed an anonymous questionnaire on age, gender, and clinical symptoms, such as seasonal rhinitis, perennial rhinitis, asthma, and eczema, and underwent an ImmunoCAP Rapid test. We calculated the prevalence of sensitization within subgroups of patients reporting allergic disorders, such as rhinitis, asthma, and eczema. Results: Questionnaires and ImmunoCAP Rapid tests of 1513 medical students were analyzed. The participants' self-reported presence of seasonal/perennial rhinitis, asthma, and eczema was compared to the presence of sensitization. Data of 1467 subjects could be analyzed. Seasonal rhinitis was the most common symptom, followed by eczema, asthma, and perennial rhinitis. The participants were differentiated into 16 subgroups according to the combined clinical manifestations of the different symptoms and association to sensitization within subgroups. The prevalence of sensitization ranged from 18% in subjects reporting only eczema without any other symptom to 100% in those reporting to have asthma, seasonal/perennial rhinitis, and eczema together. In subjects reporting no sign or symptom at all, the prevalence of sensitization was 19%. Seasonal rhinitis was the strongest single predictor for sensitization with the highest proportion of sensitized participants in all symptom combinations (67%-100%), followed by perennial rhinitis (31%-100%), asthma (30%-100%), and eczema (18%-100%). Conclusion: Rhinitis most often is associated with allergen sensitization, and the probability of sensitization is substantially enhanced by co-occurrence of asthma. A careful assessment of clinical signs and symptoms is important and enables the selection of patients in whom targeted diagnostic analysis and therapy is appropriate. Trial registration: retrospectively registered by the Cantonal Ethics Committee Zurich on 22.01.2016; Nr: 08-2016.

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# Relationship Between Rhinitis, Asthma, and Eczema and the Presence of Sensitization in Young Swiss Adults

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## Abstract

**Background:** Rhinitis is a very common disease with allergies being the most frequent causative factor. It can co-occur together with asthma and eczema in atopic as well as in nonatopic patients.

**Objectives:** To assess the prevalence of allergic sensitization within patient groups with rhinitis in consideration of the co-occurring disorders of asthma and eczema.

**Methods:** Students of the third year of medical school completed an anonymous questionnaire on age, gender, and clinical symptoms, such as seasonal rhinitis, perennial rhinitis, asthma, and eczema, and underwent an ImmunoCAP Rapid test. We calculated the prevalence of sensitization within subgroups of patients reporting allergic disorders, such as rhinitis, asthma, and eczema.

**Results:** Questionnaires and ImmunoCAP Rapid tests of 1513 medical students were analyzed. The participants' self-reported presence of seasonal/perennial rhinitis, asthma, and eczema was compared to the presence of sensitization. Data of 1467 subjects could be analyzed. Seasonal rhinitis was the most common symptom, followed by eczema, asthma, and perennial rhinitis. The participants were differentiated into 16 subgroups according to the combined clinical manifestations of the different symptoms and association to sensitization within subgroups. The prevalence of sensitization ranged from 18% in subjects reporting only eczema without any other symptom to 100% in those reporting to have asthma, seasonal/perennial rhinitis, and eczema together. In subjects reporting no sign or symptom at all, the prevalence of sensitization was 19%. Seasonal rhinitis was the strongest single predictor for sensitization with the highest proportion of sensitized participants in all symptom combinations (67%–100%), followed by perennial rhinitis (31%–100%), asthma (30%–100%), and eczema (18%–100%).

**Conclusion:** Rhinitis most often is associated with allergen sensitization, and the probability of sensitization is substantially enhanced by co-occurrence of asthma. A careful assessment of clinical signs and symptoms is important and enables the selection of patients in whom targeted diagnostic analysis and therapy is appropriate.

**Trial registration:** retrospectively registered by the Cantonal Ethics Committee Zurich on 22.01.2016; Nr: 08-2016.

## Keywords

allergic rhinitis, nonallergic rhinitis, seasonal rhinitis, perennial rhinitis, asthma, eczema, sensitization, allergic disorders, adults, symptom combinations

## Introduction

Rhinitis is a common chronic disorder, which is commonly divided into allergic and nonallergic rhinitis with a prevalence of about 30% and 10%, respectively.<sup>1–4</sup> While allergic rhinitis is associated with defined allergic trigger factors and specific IgE antibodies, non-allergic rhinitis includes vasomotor, occupational,

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hormonal, atrophic, iatrogenic, idiopathic, or infectious entities.<sup>4–7</sup> The similar phenotype of different underlying endotypes of rhinitis makes a timely diagnosis and specific therapy often difficult. This might explain why in 35% to 40% of patients with rhinitis the disease is not controlled, which results in elevated medical and socioeconomic costs.<sup>8–15</sup> Rhinitis often co-occurs with asthma and eczema and is often associated with atopy. But these allergic disorders also co-occur in nonatopic patients more often than can be expected to happen by chance.<sup>16,17</sup> A clinician should aim to distinguish allergic versus nonallergic rhinitis early as there are different treatment options available. For this study, we evaluated a selected, homogeneous population of 1683 Swiss medical students with an accumulation of risk factors for allergic disorders including higher socioeconomic status, completion of higher education, and urban life style.<sup>18–20</sup>

We sought to determine whether a thorough patient history including the clinical manifestations of rhinitis, asthma, and eczema helps to differentiate allergic rhinitis from nonallergic rhinitis. We assessed the prevalence of allergen sensitization according to the co-occurrence of the clinical manifestations of rhinitis, asthma, and eczema.

## Materials and Methods

The local Ethical Review Board of Zurich assessed the protocol of this study and offered a waiver (#8-2016). The study strictly adhered to the principles of good clinical practice and the ethical standards outlined in the Declaration of Helsinki.<sup>21</sup> The reporting guidelines for observational studies (STROBE) were applied.<sup>22</sup>

### Participants

From 2007 to 2015, all third-year medical students at the University of Zurich who attended the practical course in immunology were included, forming 9 annual cohorts. No exclusion criteria were imposed. In Switzerland, medical students usually study for 6 years after completing secondary school at an age of 18 years on average. Zurich University has the largest medical school in Switzerland, with about 220 students per clinical year. About 10% of students are from abroad. The number of inhabitants living in the catchment area for medical students at the University of Zurich is approximately 3 million. This corresponds to about 40% of the Swiss population. The proportion of female students has steadily increased and surpassed the 50% margin in 2009.

### Data collection

We secured information from a self-reported questionnaire on age, gender, and occurrence of seasonal or perennial rhinitis, asthma, and eczema from all participants.

Each student tested his or her blood during the practical course in immunology, using the ImmunoCAP Rapid test kit, a qualitative point-of-care test (Thermo Fisher Scientific Inc, Waltham, MA) according to the manufacturer's instructions and watching a short film sequence (<http://www.phadia.com/en/Products/Allergy-testing-products/ImmunoCAP-Rapid>). In addition, senior staff of the University Clinic for Immunology supervised testing. We entered anonymized personal data and the results from blood tests into an electronic database for statistical analysis.

Specific IgE antibodies against the 10 common aeroallergens, cat dander (e1), birch (t3, *Betula verrucosa*), mugwort (w6, *Artemisia vulgaris*), timothy grass (g6, *Phleum pratense*), cockroach (i6, *Blatella germanica*), dog dander (e5), olive (t9, *Olea europaea*), wall pellitory (w21, *Parietaria judaica*), house dust mite (d1, *Dermatophagoides pteronyssinus*), and mold (m6, *Alternaria alternata*) were measured. The 2007 test (ImmunoCAP Rapid wheeze/rhinitis child) contained egg white (f1) and cow's milk (f2) instead of cockroach and mold.

All participants were verbally informed and gave their oral informed consent in handing in the questionnaire and the test results.

### Definitions

We defined atopy as a sensitization to any of the tested allergens. Sensitization to olive pollen was interpreted as a sensitization to ash pollen due to a cross-reaction of the specific IgE antibodies.<sup>23</sup>

The occurrence of atopic diseases, namely rhinitis, asthma, and eczema, was assessed by self-reported answers to the questions: "Do you suffer from seasonal/perennial rhinitis, asthma or eczema?" We postulated that third-year medical students have the necessary medical knowledge to answer these questions.

### Subgroups According to Clinical Symptoms and State of Sensitization

We defined 16 different subgroups reflecting all possible combinations of the different clinical phenotypes consisting of seasonal and perennial rhinitis, asthma, and eczema. Association to sensitization was evaluated for each subgroup.

## Statistical Analysis

Interval scaled variates were summarized with means and standard deviations or medians and interquartile ranges (IQRs), where appropriate. Dichotomous variates were described as ratios and percentages. We performed all analyses using the Stata 14.2 statistics software package (StataCorp LP, College Station, TX)

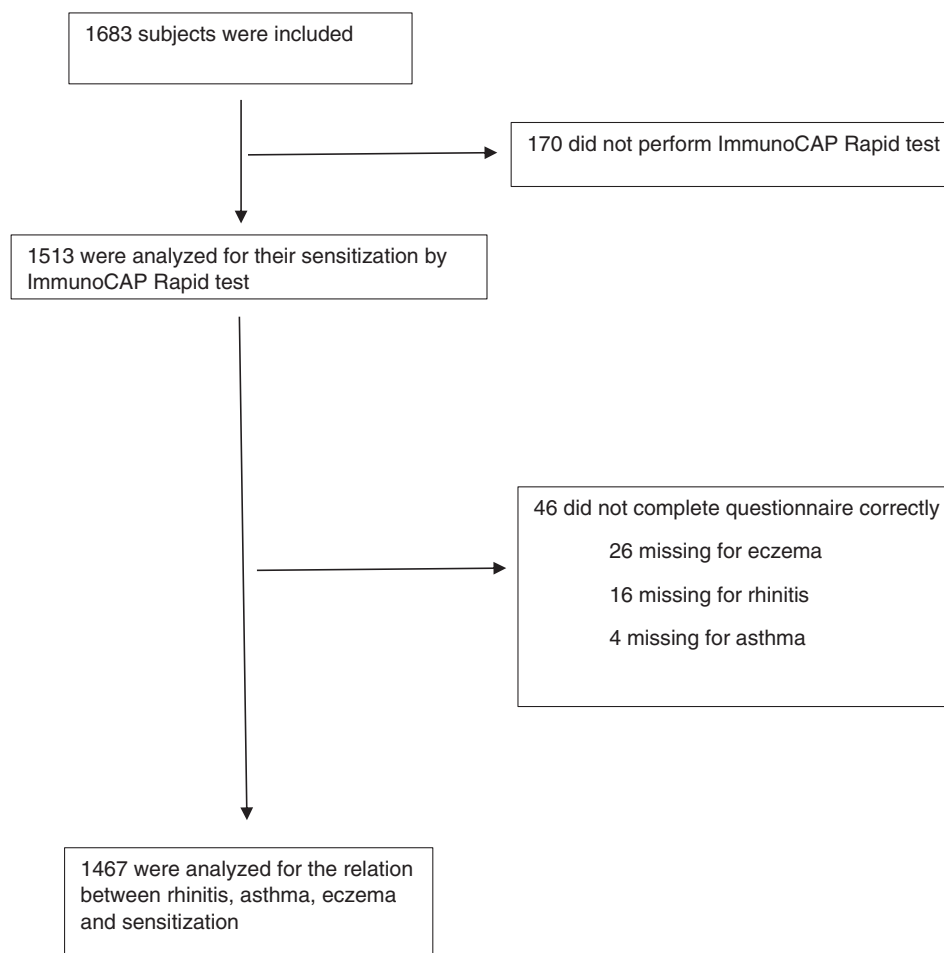
## Results

From 1683 third-year medical students assessed between 2007 and 2015, the ImmunoCAP Rapid test results were available in 1513 participants (Figure 1). The median cohort size across annual courses was 215 students, (IQR: 193–222) and the proportion of female students ranged from 43% to 62%. The mean age ranged from 22.4 years to 23.3 years. Overall sensitization was 40% (604 of 1513). Sensitization to grass pollen was most prevalent followed by birch pollen and house dust mites (Table 1).

Sensitization rate and clinical data on rhinitis, asthma, and eczema were available in 1467 subjects (Figure 1). Seasonal rhinitis was the most prevalent symptom in 546 (37%) subjects followed by eczema, asthma, and perennial rhinitis. Comparing atopic with nonatopic subjects, all symptoms except for eczema were more prevalent in atopics (Table 2).

## Subgroup Analysis

The prevalence of sensitization within subgroups suffering from single symptoms ranged from 18% (17 of 95) in subjects reporting only eczema, to 30% (10 of 33) with asthma, to 30% (8 of 26) with perennial rhinitis, and to 68% (228 of 335) with seasonal rhinitis. In subjects with co-occurrence of 2 allergic disorders, a sensitization rate of 76% (142 of 186) was documented. In participants with perennial or seasonal rhinitis and asthma sensitization rate was 60% (6 of 10) and 84% (62 of 74), with perennial or seasonal rhinitis and eczema 67% (4 of 6) and 71% (48 of 68), with seasonal and perennial rhinitis 89% (17 of 19) and with asthma and eczema 55% (5



**Figure 1.** Included and analyzed participants.

of 9), respectively. Sensitization rate in participants with 3 allergic disorders was 78% (185 of 237). Seasonal and perennial rhinitis with eczema or asthma were sensitized in 67% (4 of 6) and 85% (11 of 13), and asthma and eczema with seasonal or perennial rhinitis in 89% (25 of 28) and 100% (1 of 1), respectively. Highest sensitization rate was assessed in subjects reporting to have seasonal/perennial rhinitis, asthma, and eczema together with

100% (3 of 3). In subjects reporting no sign or symptom at all, the prevalence of sensitization was 19% (140 of 741).

From the investigated population, 49% (726 of 1467) suffered from at least 1 allergic disorder and 16% (237 of 1467) from at least 2 or 3 allergic disorders. Rhinitis co-occurred more often together with asthma than with eczema. Prevalence of sensitization across all subgroups with the combination of the different comorbidities is shown in Table 3.

**Table 1.** Characteristics of the 9 Study Cohorts From 2007 to 2017.

Parameter	Frequency
Cohort size 2007–2015	1513
Median cohort size	215 (IQR: 192–222)
Female subjects	44%–62%
Mean age, years	22.4–23.3
<i>Frequency of sensitization</i>	
Sensitization	604 (40%)
Cat dander (e1)	106 (7%)
Birch (t3)	231 (15%)
Mugwort (w6)	42 (3%)
Timothy grass (g6)	416 (27%)
Cockroach (i6)	17 (1%)
Dog dander (e5)	25 (2%)
Olive (t9)	179 (12%)
Parietaria (w21)	29 (2%)
House dust mite (d1)	265 (17%)
Mold ( <i>Alternaria</i> , m6)	28 (2%)

Abbreviation: IQR: interquartile range.

Sensitization measured by ImmunoCAP Rapid test.

**Table 2.** Comorbidities With the Individual Ratio of Atopic and Nonatopic Subjects (N = 1467).

	All	Atopic	Nonatopic
Seasonal rhinitis	546 (37%)	398 (73%)	148 (27%)
Perennial rhinitis	84 (6%)	53 (63%)	31 (37%)
Asthma	161 (11%)	117 (72%)	44 (28%)
Eczema	216 (15%)	106 (49%)	110 (51%)

## Discussion

In this study, we analyzed the sensitization rate and co-occurrence of the allergic disorders rhinitis, asthma, and eczema in a large cohort of Swiss medical students. The documented sensitization rate of 40% corresponds with previously published data from industrialized countries.<sup>24–26</sup> Grass pollen was the most frequently detected allergen followed by house dust mites and tree pollen which is in line with other studies.<sup>24,25</sup> Although this well-educated study population in particular living in urban environment has an increased risk to suffer from allergies,<sup>18–20</sup> the prevalence of atopic disorders was comparable with the current literature in which different risk profiles were not addressed. Recent evidence suggests that rhinitis, asthma, and eczema are coexisting disorders becoming more prevalent with increasing age.<sup>16,27</sup> They are strongly associated with specific IgE antibodies but also co-occur in nonsensitized individuals.<sup>17,28</sup> Seasonal rhinitis is the most common symptom of these allergic disorders in atopic and nonatopic subjects with a prevalence of 10% to 30%. Comparing seasonal and perennial rhinitis, the former is clearly more associated with atopy (Tables 2 and 3).<sup>3,4,17,27,29</sup> The prevalence of the allergic disorders in our cohort for allergic seasonal rhinitis with 27%, allergic asthma with 8%, and atopic eczema 7% is in line with the current literature (Table 2).<sup>27,30–33</sup>

The strongest single predictor for allergen sensitization was seasonal rhinitis (68%), and the probability of

**Table 3.** Subgroup Analysis of Combined Occurrence of Allergic Disorders (N = 1467).

				Perennial Rhinitis			
				No		Yes	
				Seasonal Rhinitis		Seasonal Rhinitis	
				No	Yes	No	Yes
Asthma	No	Eczema	No	741 (19%)	335 (68%)	26 (30%)	19 (89%)
			Yes	95 (18%)	68 (71%)	6 (50%)	6 (67%)
	Yes	Eczema	No	33 (30%)	74 (84%)	10 (60%)	13 (85%)
			Yes	9 (55%)	28 (89%)	1 (100%)	3 (100%)

Values in parenthesis represent the number of sensitized participants.



sensitization is enhanced when additional symptoms with perennial rhinitis and asthma co-occur. However, eczema was a weak predictor for sensitization (Table 3). This is most probably explained by the sensitization path occurring more often by inhalant allergens via the respiratory tract mucosa and not via the skin.<sup>34</sup>

The lack of detailed information about the subjects' genetic background, place of birth, and the time point when sensitization and/or allergic symptoms were first diagnosed is a potential limitation of this study. Self-reporting of symptoms carries the risk of reporting bias. The possibility of a different understanding of how to make a diagnosis of rhinitis, asthma, and eczema is a potential limitation, and we cannot fully rule out that such bias occurred in our study. On the other hand, it can be expected that third-year medical students have the necessary medical knowledge to indicate whether they are suffering from seasonal/perennial rhinitis, asthma, or eczema.

In conclusion, patients with rhinitis have a high probability of suffering from allergies. Co-occurrence of asthma enhances this probability substantially. In all patients with rhinitis as a single clinical symptom or combined with asthma and/or eczema an allergologic workup is reasonable. This enables an early and targeted therapy.

### Ethical Approval

The local Ethical Review Board of Zurich assessed the protocol of this study and offered a waiver (#8-2016).

### Statement of Human and Animal Rights

The study strictly adhered to the principles of good clinical practice and the ethical standards outlined in the Declaration of Helsinki. The reporting guidelines for observational studies (STROBE) were applied.

### Statement of Informed Consent

All participants were verbally informed and gave their oral informed consent in handing in the questionnaire and the test results.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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